LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

Monrovia, Liberia
Cell: +231-888-140-555 / +231-777-140-555
Email: info@lmhra.gov.lr; Website: www.lmhra.gov.lr

REGULATIONS ON PHARMACOVIGILANCE IN LIBERIA

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Declaration

This regulation, made in the fulfilment of **Part III, count 5** and **Part IV, Section 2, count 1h** of the Act of 2010, establishing the Liberia Medicines and Health Products Regulatory Authority (LMHRA), which authorizes the Authority to conduct Pharmacovigilance of medicines and health products within the borders of the Republic of Liberia. The management, with approval from the Board of Directors, hereby promulgates this regulation designed for the conduct of Pharmacovigilance.

ABBREVIATIONS

ACT	**:**	Artemisinin based Combination Therapy
ADR	**:**	Adverse Drug Reaction
AE	**:**	Adverse Events
AEFI	**:**	Adverse Events Following Immunization
CIT	**:**	County Investigation Team
CHT	**:**	County Health Team
CT	**:**	Clinical Trials
DDFP	**:**	Drug Depot Focal Person
DSUR	**:**	*Development safety Update Report*
ECCT	**:**	Expert Committee on Clinical Trials
EDP	**:**	Essential Drugs Program
EMA	**:**	European Medicines Agency
ESRP	**:**	Expert Safety Review Panel
GVP	**:**	Good Pharmacovigilance Practice
ICH	**:**	International Conference on Harmonization
LMHRA	**:**	Liberia Medicines and Health Products Regulatory Authority
MAH	**:**	Marketing Authorization Holder
MOH	**:**	Ministry of Health
NACP	**:**	National AIDS Control Program
NMCP	**:**	National Malaria Control Program
NPC	**:**	National Pharmacovigilance Center
NTLCP	**:**	National Tuberculosis & Leprosy Control Program
OTC	**:**	Over the counter
LPB	**:**	Pharmacy Board of Liberia
PTC	**:**	Pharmacovigilance Technical Committee
PMS	:	Post Market Surveillance
PV	**:**	Pharmacovigilance
SAC-PV	:	Scientific Advisory Committee on Pharmacovigilance
UMC	**:**	Uppsala Monitoring Center
UMC-A	**:**	Uppsala Monitoring Center - Africa
WHO	**:**	World Health Organization
WHO-CC	**:**	World Health Organization Collaborating Centers

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We herein acknowledge the hard-working committee for their tireless efforts in the development of the first version of the Regulation on Pharmacovigilance in Liberia. This regulation provides the legal basis on the conduct of Pharmacovigilance in Liberia.

The Global Health Protection Program (GHPP) through its Paul Ehrlich Institut Office have provided technical support in the review and modification of this regulation

The Department of Clinical Trials, Pharmacovigilance and Medicines Information of the Liberia Medicines and Health Products Regulatory Authority (LMHRA) have worked along with the VaccTrain Team of the Paul Ehrlich Institut to develop the first version of this regulation and other technical related PV documents.

I am pleased to express my profound gratitude to the committee; led by Dr. James D. K. Goteh (Head of Department) and the committed team of experts, Dr. Juwe D. Kercula, Dr. Margaret T. Massaquoi, Pharm Sancee G. Gray, and the LMHRA Management team for the level of support and resources exerted in the development of this vital document. The Scientific Advisory Committee on Pharmacovigilance contribution to this work is highly noted.

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With my highest regards, I remain.

Hon Luke L. Bawo, Jr.
Managing Director
LMHRA
Email: lukebawo@gmail.com
Tel: +231-777-932-220

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PART I

Section 1: Citation

These Regulations shall be cited as the Liberia Pharmacovigilance Regulations for all medicines and health products, including vaccines, biological and gene therapy products, and shall be deemed to come into operation on 28/May/2025.

Section 2: Scope

Section 3: Application

These Regulations shall apply to all medicines and health products within the borders of Liberia.

Section 3: Terms and definitions

In these Regulations, unless the context otherwise requires –

1. ***Act*** - means the Liberia Medicines and Health Products Regulatory Authority (LMHRA) Act;
2. ***Authority*** – means the Liberia Medicines and Health Products Regulatory Authority.
3. ***Active surveillance*** - means active measures taken to monitor adverse events;
4. ***Adverse Drug Reaction (ADR)*** - means a response to a medicine which is noxious and unintended, and which occurs at a dose normally used in humans for prophylaxis, diagnosis, or therapy of disease or the modification of physiological function;
5. ***Adverse Events (AE)*** - means any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the product, whether or not related to the product.
6. ***Audit*** - means a systematic, disciplined, independent, and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control, and governance processes;
7. ***Cosmetic product safety report*** - means all available data on the undesirable effects and serious undesirable effects to the cosmetic product or, where relevant, other cosmetic products, including statistical data;
8. ***Development safety Update Report (DSUR)*** - a periodic report on a drug under development (including marketed products that are under further studies) deemed to be recognized by the Authority.
9. ***Healthcare providers*** - means medically qualified persons including physicians, dentists, pharmacists, nurses, Physician assistant , pharmaceutical technicians, laboratory technicians, laboratory technologists and traditional medicine practitioners;

10. ***Herbal medicines*** - includes crude plant materials such as leaves, flowers, fruit, and seed, herbal materials such as fresh juices, gums, fixed oils, essential oils, and dry powders, herbal preparations such as comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials and finished herbal products such as dosage forms preparations made from one or more herbs that may contain excipients used for therapeutic purposes;
11. ***Individual Case Safety Report (ICSR)*** – refers to the format and content for the submission of an individual report of suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect medicinal product.
12. ***Lack of efficacy*** - means unexpected failure of a medicines or health product to produce the intended effect as determined by previous scientific investigation;
13. ***Marketing Authorization Holder (MAH)*** - means an individual or a corporate entity responsible for placing a pharmaceutical product in the market;
14. ***Medication error*** - means any unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Such events may be related to professional practice, health care products, procedures and systems, including prescribing; order communication; product labelling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; storing; and use; thereby present a major public health burden.
15. ***National Pharmacovigilance Centre (NPC)*** - means a single, governmentally recognized Centre established under regulation 4 of these Regulations;
16. ***Over dosage*** - means accidental or intentional use of a drug or medicine in an amount that is higher than normally used.
17. ***Pharmacovigilance (PV)*** - means science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems;
18. ***Pharmacovigilance system master file*** - means a file ascribed to in preceding regulations is an accuracy reflection of information of the Pharmacovigilance system.
19. ***Public Health Programs*** - means programs under the Ministry of Health responsible for health including National AIDS Control Program (NACP), National Malaria Control Program (NMCP), National Tuberculosis and Leprosy Program (NTLP) and Expanded Program for Immunization (EPI);
20. ***Periodic Benefit-Risk Evaluation Report (PBRER)*** - means a comprehensive safety evaluation report produced by the Marketing Authorization Holders (individuals or business that is granted authorization to market the medicine) at defined time points after a medicine has been given;
21. **Products regulated** - means medicines and health products that require authorization before they can be sold;

22. ***Periodic Safety Update Report (PSUR)*** - means an update of the world-wide safety experience of a product obtained at defined times post marketing authorization.
23. ***Risk-benefit balance*** - means an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health
24. ***Risk Management System*** - means a set of Pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions;
25. ***Risks related to use of a medicinal product*** - means any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment;
26. ***Serious Adverse Event (SAE)*** - means adverse event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect;
27. ***Serious Adverse Drug Reaction*** - means an adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect;
28. ***Serious undesirable effects*** - means an undesirable effect which results in temporary or permanent functional incapacity, disability, hospitalization, congenital anomalies, or an immediate vital risk or death;
29. ***Life-threatening*** - means a reaction in which the patient was at risk of death at the time of the reaction but not including a reaction that hypothetically might have caused death if more severe;
30. ***Signal*** - means reported information on a possible causal relationship between an adverse event and a medicine the relationship being unknown or incompletely documented previously;
31. ***Summary Product Characteristics (SmPC)*** - means a document describing the properties and the officially approved conditions of use of a medicine. An SmPC forms the basis of information for healthcare professionals on how to use the medicine safely and effectively;
32. ***Unexpected adverse drug reaction*** - means an adverse reaction, the nature, severity or outcome of which is not consistent with domestic labelling, marketing authorization, or the SmPC.

PART II

Section 1: Pharmacovigilance System

1. Organization of the Pharmacovigilance System

a. There is a national Pharmacovigilance System established and operated by the Authority.
b. The National Pharmacovigilance System shall comprise
    i. The National Pharmacovigilance Center was established under the Authority.
    ii. Scientific Advisory Committee for Pharmacovigilance;
    iii. Regional and hospital investigation teams; and
    iv. A focal person at the Regional offices and Health Facilities.
c. Key stakeholders of the National Pharmacovigilance System may include
    i. A representative of the Ministry of Commerce and Industry;
    ii. A representative from the Ministry of Health;
    iii. A representative from the Ministry of Agriculture;
    iv. The Liberia Chamber of Commerce;
    v. Health training institutions
    vi. Health research institutions
    vii. Manufacturers
    viii. Suppliers
    ix. Consumer associations
    x. Members of the media
    xi. Any other members as the Agency may define.
d. To prevent direct or indirect hazards to human health, the Agency shall
    i. record and evaluate risks associated with the administration of medicines;
    ii. record suspected cases of adverse drug reactions, interactions with other products, and adulterations and-
    iii. monitor the outcome of the risk minimisation measures contained in the risk management plans, and
    iv. assess updates to the risk management system;
    v. record potential risks to the environment as a consequence of the use of a veterinary medicine; and
    vi. Co-ordinate the measures to be adopted to address any risks in accordance with these Regulations.
e. The Agency shall cooperate with the World Health Organisation and other regional and international medicines regulatory authorities that keep records on medicines risks.

f. The Agency shall inform the public about medicines that pose health risks and measures that have been developed to mitigate the risks.
g. The Agency shall conduct regular audits of its Pharmacovigilance System

2. Establishment of National Pharmacovigilance Center and Regional Pharmacovigilance Center

a. The Authority shall establish and maintain a National Pharmacovigilance Center (NPC) located at the headquarters of the Liberia Medicines and Health Products Regulatory Authority (LMHRA). The NPC shall have designated staff (at least 4 full-time), well-defined structures, provide stable funding for PV centers and PV-related activities in the country, define clear mandates, roles, and responsibilities, working instructions, and monitor its implementation.
b. The Authority shall establish Regional Pharmacovigilance Centers (RPC) across the country for the appropriate coordination of Pharmacovigilance activities in the regions.
c. The Authority shall supervise and coordinate the work of regional PV centers. Conduct training, performance evaluation, and inspection, if relevant, to strengthen the PV regulatory network in the country.

3. Functions of the National Pharmacovigilance Center and Regional Pharmacovigilance Center

a. <u>The function of the RPCs shall include</u>
   i. Collect and collate adverse drug reaction (ADR) reports from health facilities;
   ii. Ensure the ADR report meets the minimum requirements for submission to the NPC;
   iii. To submit ADR Reports to the NPC;
   iv. Provide feedback to health facilities that reported ADRs.
b. <u>The functions of the NPC shall include:</u>
   i. To regulate all matters relating to efficacy, quality, and safety of medicinal and other related products in Liberia;
   ii. To develop pharmacovigilance procedures and guidelines for stakeholders involved in pharmacovigilance and clinical trials in the Liberian health system;
   iii. To develop and update the regulatory framework that defines the provisions for conducting, monitoring, and management of all PV activities to ensure quality, safety, and efficacy of medicines and health products, including vaccines, biological and gene therapy products in Liberia;
   iv. To adopt and adapt international regulations and guidelines as and when necessary, as well as to rely on other WHO-listed NRAs for regulatory decision-making and actions.
   v. To promote pharmacovigilance in the country, notably, to collect and manage (ADR reports, reports of medication errors and suspected substandard and falsified drugs;
   vi. To collaborate and harmonize with existing ADR and adverse event following immunization (AEFI) report collection activities within the country (e.g. **National**

Disease Control Programs, Ministry of Health), as well as international studies that are monitoring ADRs / AEFIs in defined patients or populations;

vii. To establish and sustain a functional national database for collating, managing and retrieving ADRs/ AEFIs reports.

viii. To request conduct of Post-Authorization Safety and Efficacy Studies (PASS/PAES) to ensure safety and efficacy of authorized medicinal products, including vaccines, biologicals, and gene therapy products.

ix. To establish sentinel sites for vaccine safety monitoring and request to conduct active surveillance of AEFIs and adverse event of special interest (AESIs).

x. To establish a spontaneous reporting system ensuring post-authorization safety of MPs, including vaccines, biologicals, and gene therapy products.

xi. To stimulate spontaneous reporting by encouraging health care professionals (HCPs), patients, all relevant stakeholders to report AEs, ADRs, AEFIs, and AESIs.

xii. To request the conduct of epidemiological studies by MAHs to test the safety or efficacy of products.

xiii. To conduct causality assessment on serious AEs, ADRs, AEFIs, and AESIs in Liberia;

xiv. To conduct relevant research and coordinate signal detection and management activities;

xv. To communicate with all relevant stakeholders on medicines safety issues in Liberia as well as in other territories;

xvi. To coordinate the quarterly meeting of the Scientific Advisory Committee (SAC) on PV;

xvii. To provide training for all healthcare workers in Liberia on ADRs, AEFI, and AESI reportage;

xviii. To manage, assess, analyze, identify signals, and compile reports for onward submission to the Scientific Advisory Committee on PV;

xix. To identify quality problems in medicines resulting in ADRs, to support the identification of medicine quality issues in collaboration with the LMHRA respective departments, Department of Inspectorate, and Post Market Surveillance, Quality Control lab and Evaluation & Registration;

xx. To provide outcome(s) of the causality assessments of ADRs and AEFIs to the Managing Director for onward regulatory action(s);

xxi. To submit medicines safety reports to the West Africa Health Organization (WAHO) and WHO Program for International Drug Monitoring;

xxii. To ensure implementation of Risk management and Risk minimization plans by MAHs and all concerned stakeholders;

xxiii. To develop preparedness plans to address public health emergency preparedness, including vaccine safety crises;

xxiv. To implement methods and tools for comprehensive monitoring and investigation of AEs/ADRs/AEFIs/AESIs, ensuring safety and efficacy and quality of medicinal products in the country;

xxv. To develop institutional development plans (**IDPs**) for **NPC** and regional PV centers;

xxvi. To monitor the performance of NPC and regional PV centers according to developed IDPs and key performance indicators (**KPI**s);

xxvii. To periodically evaluate and revise the IDPs to ensure continuous quality improvement of national pharmacovigilance and vaccine safety activities.

xxviii. To establish a partnership with international bodies (**NRAs of ECOWAS region, WAHO, WHO AFRO, WHO UMC, AVAREF, AMRH**) for support and implementation of PV activities;

xxix. To develop a communication strategy for routine communication and crisis communication between PV stakeholders.

xxx. To communicate safety information related to the regulated medicinal products, including vaccines, biological and gene therapy products to all concerned stakeholders HCPs, including manufacturers, public, media and ensure feedback mechanism.

xxxi. To communicate on identified risks and benefits, encouraging the monitoring of AEs, ADRs, and AEFIs by all concerned stakeholders.

xxxii. To provide effective communication on aspects related to medicine safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines

xxxiii. To develop and maintain drug utilization information.

xxxiv. To identify issues associated with the unregulated prescribing and dispensing of medicines and health products.

4. Establishment of Scientific Advisory Committee for Pharmacovigilance

a. There shall be established a committee to be known as a Scientific Advisory Committee for Pharmacovigilance (SAC-PV), and its main purpose will be to provide recommendations to the Managing Director on Pharmacovigilance-related safety issues.
b. The Managing Director shall, upon such recommendations from the Committee, cause the action on any technical matter to be taken or implemented as the case may be.
c. Composition of SAC-PV Members: a broad range of disciplines, incorporating many aspects of safety monitoring of medicinal products (including vaccines) during clinical applications. As far as possible, the SAC-PV shall be balanced in terms of professional bodies (academia, clinical practice, research institute, government, and private sector; disease specialization; other relevant expertise, ethics and regulatory affairs, and gender.
d. The membership of the SAC-PV shall comprise eleven (11) members who shall serve for a period of two (2) years, which may be extended once for a further period of up to four years. This committee may co-opt certain experts to attend SAC meetings and/or carry out particular tasks and activities as the need arises.

e. The SAC-PV shall have no executive function, and SAC-PV members are not LMHRA employees. The SAC's role is solely to provide technical advice and recommendations to the LMHRA on safety issues.
f. Quorum, The SAC-PV shall have a quorum when a minimum of two-thirds of the members are present. If decision-making requires voting, the SAC-PV members, including the Chairperson, shall have a vote, and a simple majority shall decide. Dissenting opinions, including the reasons for dissent, shall be recorded in the minutes. The Managing Director of the LMHRA and the Secretariat to the SAC-PV shall have NO VOTING rights.

5. Roles of the Scientific Advisory Committee on Pharmacovigilance

The committee shall:

a. Conduct final review of all PV reports previously classified by the Secretariat of the PV unit.
b. regularly review and advise the Authority on the Pharmacovigilance system in the country and make recommendations regarding its maintenance and improvement;
c. perform causality assessment on serious AEs, ADRs, AEFIs or AESIs in relation to the use of medicinal products, including vaccines, biological and gene therapy products;
d. Perform review of ICSR reports, PSUR, risk management plans, and risk minimization plans, DSUR
e. Perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance of medicinal products.
f. Conduct coordinated or joint review of safety issues in CTs together with the Clinical Trials Advisory Committee, if needed
g. make recommendations to the Authority regarding actions the Authority may take to resolve issues or concerns related to the conduct of Pharmacovigilance; the final responsibility for issuing medicinal products safety relating issues should remain with the Authority
h. Recommend publication (Support LMHRA in publishing) information on safety/efficacy concerns, case reports, as well as its risk or benefit evaluations in medical and scientific journals;
i. advise the Authority on matters relating to GVP inspections conducted by the Authority
j. Perform any other functions that are ancillary to the attainment of the objectives of the Committee.

6. Establishment of Pharmacovigilance system for manufacturers and marketing authorization holders

a. All manufacturers and Marketing Authorization holders shall establish a Pharmacovigilance system for the following as per the regulation:
b. Establishing and maintaining continuous collection, handling, evaluation and reporting of ADRs/AEFIs
c. Performing signal detection and management of detected signals.
d. Establishing and maintaining risk management and risk communication plans
e. Preparing and submitting periodic safety reporting (PSUR/DSUR)
f. Conducting Post authorization safety and efficacy studies
g. Any additional PV related purposes, as and when deemed necessary for safety monitoring of medicinal products.
h. The system shall be comprised of structures, processes and outcomes, which shall be adaptable to public health emergencies or development plans.

7. Pharmacovigilance Quality System

a. For the purpose of Good Pharmacovigilance Practice in Liberia, every PV system shall have a quality PV system.
b. The Pharmacovigilance quality system shall involve quality planning, adherence, control, assurance and improvements.
c. The objectives of the quality system shall be to comply with legal requirements, prevention from adverse reactions, promotion of safe and effective use and protection of patients and public health.
d. The manufacturer or marketing authorization holder shall maintain the quality system according to Quality Management System requirements (WHO GL, ISO QMS- see Annex I) by performing the following -
    i. The manufacturer or MAH shall designate a qualified person responsible for Pharmacovigilance (QPPV) if the main pharmacovigilance activities are performed within Liberia or a local PV responsible person, if the main pharmacovigilance activities are performed outside Liberia. The QPPV or local person responsible for PV shall operate within Liberia and maintain the PSMF according to the PV system requirements, and respective regulations adopted by LMHRA.
    ii. Establishing and maintaining a record management system to afford handling and storage of documentation for accurate reporting, interpretation and verification;
    iii. Establishing and maintaining document control in relation to their creation, revision, approval and implementation;

iv. Ensuring continuous training of personnel relevant to the system, premises, facilities and equipment to support PV processes which are located, designed, constructed, adapted and maintained to suit their intended purpose;
v. Putting procedures and processes in place to ensure continuous monitoring of PV data and scientific evaluation of all information on the risks of products.
vi. Putting in place procedures and processes to ensure timely and effective communication internally as well as with external stakeholders on safety concerns relating to medicinal products.

e. In addition to the requirement of maintaining a quality system, manufacture or MAH should ensure:
   i. Adequate resources are available for all PV activities to be performed as legally required by the Authority.
   ii. Suitable and sufficient premises, facilities and equipment are available for PV activities to be performed as legally required;
   iii. Adequate PV compliance management;
   iv. Adequate and appropriate record management of all PV related information, including ensuring confidentiality.
   v. Review of the PV system including its quality system at regular intervals in a risk-based manner to verify its effectiveness and introducing corrective action and prevention action (CAPA) where necessary;
f. identification and investigation of concerns regarding suspected non-adherence to the requirements stated in this document and implementing CAPA and escalating actions as necessary;
g. Audits are performed

8. Training of personnel for Pharmacovigilance

a. Every Market Authorization Holder or manufacturer shall provide initial and continued training to personnel involved in implementation of Pharmacovigilance activities.
b. The training plans shall be based on the roles and responsibilities of the personnel and respective records shall be maintained.
c. The training shall also apply to external vendors and partners and shall be clearly stipulated in the contractual agreements and audited regularly.

9. Facilities and equipment for Pharmacovigilance

The market authorization holder and manufacturer shall maintain facilities and equipment for Pharmacovigilance.

10. Record management and documentation

a. Every manufacturer and marketing authorization holder shall keep and maintain a record management system on Pharmacovigilance information reflecting to PV system objectives, according to Quality Management System requirements (WHO GL, ISO QMS- see Annex I)
b. The information in the record management system shall be handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.
c. The Marketing Authorization Holder shall ensure that the analytical dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection by the Authority.
d. The system shall include mechanisms for timely retrieval, traceability, follow-up and communication of safety information.
e. In case of outsourcing Pharmacovigilance activities to a third-party person or external organization, a detailed Pharmacovigilance contract or agreement shall be in place.
f. Keep appropriate structures and processes in place to ensure that Pharmacovigilance data and records are protected from destruction throughout the period in which the product will be in the Liberian market.
g. All elements, requirements, and provisions adopted for the quality system shall be documented in a systematic and orderly manner in written policies and procedures.
h. Manufacturers, Market Authorization Holders, and all parties involved in Pharmacovigilance activities who use an electronic system shall ensure the following-
    i. Data of the validation of system(s) used for recording, evaluating, and tracking complaints and adverse reactions shall be available;
    ii. Computerized systems shall be validated to ensure that systems are periodically and suitably backed up at pre-defined intervals; and
    iii. Any changes made to the system shall be subject to a revalidation.

11. Requirements for the Pharmacovigilance plan

a. Every manufacturer and marketing authorization holder shall have a Pharmacovigilance plan that includes safety specifications.
b. The PV plan can be discussed with the Authority during product development, where practicable, prior to approval of a new product, or when a safety concern arises post-marketing.
c. The safety specifications shall include the following-
    i. Elements of the specification
    ii. Non-clinical
    iii. Clinical
    iv. Limitation of the human safety database

v. Populations not studied in the pre-approval phase
vi. Adverse events or adverse drug reactions
vii. Identified and potential risks that require further evaluation
viii. identified and potential interactions, including food-drug and drug-drug interactions
ix. epidemiology
x. pharmacological class effects
xi. summary

d. The Pharmacovigilance plan shall be based on safety specifications and shall include the following –
   i. structure of the Pharmacovigilance plan;
   ii. summary of ongoing safety issues;
   iii. routine Pharmacovigilance practices;
   iv. action plan for safety issues;
   v. summary of actions to be completed, including milestones;
   vi. Pharmacovigilance methods;
   vii. design and conduct of observational studies;
   viii. References.

12. Requirements for Pharmacovigilance System Master file (PSMF)

a. Every manufacturer and Marketing authorization holder shall maintain and make available upon request by the Authority a copy of the PSMF.
b. The PSMF shall be located in Liberia at the manufacturer's site for local manufactures, or if the main pharmacovigilance activities are performed outside Liberia, the PSMF shall be located with the QPPV or at the primary location where PV activities are conducted.
c. The PSMF shall be kept irrespective of the format (paper-based or electronic format file) and presented to the inspectors upon request.
d. During application for marketing authorization, the manufacturers and marketing authorization holders shall submit summary information about their Pharmacovigilance system, including the location of the PSMF.
e. The marketing authorization holder may subcontract certain activities of the Pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the PSMF.
f. The information in the PSMF shall be accurate and reflect the Pharmacovigilance system in place.
g. The marketing authorization holder shall, where appropriate, use separate Pharmacovigilance systems for different categories of medicinal products, and such system shall be described in a separate PSMF.

h. The PSMF shall cover all products for which the marketing authorization holder obtained a marketing authorization according to the Act.
i. The PSMF shall be stored in electronic form, provided that the media used for storage remain readable over time and a clearly arranged copy can be made available for audits and inspections.

13. Structure of the Pharmacovigilance system master file

The PSMF shall contain the following elements-

a. Information relating to the focal/qualified person responsible for Pharmacovigilance ;
b. a description of the organizational structure, a list of the sites, and Pharmacovigilance activities undertaken.
c. A description of the location, functionality, and operational responsibility for computerized systems and databases used in the Pharmacovigilance system;
d. a description of data handling and recording and of the process used for each of the Pharmacovigilance activities including the monitoring of the risk-benefit balance of the product(s), operation of the risk management system(s), collection, assessment and reporting of individual case safety reports, collection, assessment and preparation and reporting of individual case safety reports and procedures for communicating safety concerns;
e. A description of the quality system for the performance of Pharmacovigilance activities
f. A description of the activities or services subcontracted by the marketing authorization holder, where applicable.
g. Any other additional documents that the Authority deems necessary.
h. Good Distribution Practice documents: List of audits conducted and completed, and Documentation of the history of changes

14. Transfer or delegation of responsibilities

In case of transfer or delegation of responsibilities and activities concerning the PSMF, the transfer shall be documented.

15. Changes to the Pharmacovigilance System Master File

Any changes to the PSMF shall be notified to the designated focal person responsible for Pharmacovigilance/QPPV.

16. Sharing of the Pharmacovigilance system master file

In case a Pharmacovigilance system is shared, there shall be written agreements between parties on how to maintain the relevant sections within their own PSMF and accessibility of the file to all the applicable marketing authorisation holder(s).

Section 2: Pharmacovigilance responsibilities for stakeholders

1. Responsibilities for MAHs and Manufacturers

a. The holders of marketing authorizations and manufacturers shall be proactively responsible for ongoing safety monitoring of the products they place on the market.
b. The Marketing authorization holder shall be responsible for the following tasks and responsibilities:
    i. establishment and operation of a Pharmacovigilance system and quality system as prescribed under these regulations;
    ii. ensuring that structures and processes for Pharmacovigilance are in place;
    iii. preparation and maintenance of a PSMF;
    iv. Appointment of a permanent designated focal person responsible for the establishment and maintenance of the Pharmacovigilance system (QPPV), who has university qualifications, knowledge, and experience in Pharmacovigilance ;
    v. ensuring that there is access to a registered medically qualified person for clinical assessments;
    vi. ensuring that the QPPV or QPPV deputy has sufficient Authority to influence the performance of the quality system and the Pharmacovigilance activities of the Marketing Authorization Holder, including access to the PSMF;
    vii. Submission to the Authority the name and contact details of the qualified person (or QPPV deputy) responsible for Pharmacovigilance, summary of the Pharmacovigilance system, Risk Management Plans, Periodic Safety Update Reports (PSURs), Risk-benefit assessment reports (PBRERs) and reports on adverse reactions and events occurring within and outside Liberia;
    viii. development and maintenance of product-specific risk management systems and take any additional Pharmacovigilance and risk minimization actions required;
    ix. notification to the Authority of any change in details regarding the designated focal person responsible for Pharmacovigilance (or QPPV deputy) and the site master file location;
    x. The periodic reports shall be submitted to the Authority immediately upon request or in accordance with the following:
        A. where a product has not yet been placed on the market, at least every 6 months following authorization and until the placing on the market;

B. where a product has been placed on the market, at least every six months during the first two years following the initial placing on the market, once a year for the following two years, and at three yearly intervals thereafter;

C. Inform the Authority on any significant safety and product quality issues or actions taken by a foreign agency, including the basis for such actions;

D. Submit to the Authority responses to additional information requests within 14 working days from the date of the request;

E. Take any action necessary to mitigate an identified safety issue;

F. Conduct post-approval safety studies on their products as a condition of approval or long-term safety follow-up.

G. Adverse Event Reporting is the responsibility of the regulatory authority to ensure that healthcare professionals provide timely reporting of ADRs from health facilities.

H. Safety Data Management involves the effective collection, analysis, and storage of safety data that are essential for identifying potential drug-related risks and ensuring patients' safety.

I. Signal Detection Communication encompasses continuous monitoring and communication necessary to identify emerging safety concerns related to medications.

J. Compliance with Pharmacovigilance Regulations ensures the safety, efficacy, and quality of medical products.

K. Communication with the Authority is crucial for reporting safety concerns and maintaining compliance.

L. Update product labeling regularly to ensure it reflects the latest safety information to protect public health.

Responsibilities of the Qualified Person for Pharmacovigilance (QPPV)

The designated QPPV shall have the following responsibilities:

a) establishment and maintenance of the Pharmacovigilance systems

b) to provide oversight over the functioning of the system in all relevant aspects, including its quality system;s
c) to promote, maintain and improve compliance with the legal requirements;
d) to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the Pharmacovigilance system;
e) to be aware of product safety profiles, emerging safety concerns, risk management plans and minimization measures;
f) ensuring conduct of Pharmacovigilance and submission of all Pharmacovigilance - related documents in accordance with the legal requirements and Good Pharmacovigilance Practice;
g) ensuring the necessary quality, including the correctness and completeness, of Pharmacovigilance data submitted to the Authority;
h) ensuring validation of the adverse reaction database and implementation of corrective actions to address any failures and be informed of significant changes that are made to the database;
i) providing relevant information on benefit-risk evaluation to the Authority;
j) providing responses to regulatory actions in emerging safety concerns including variations, urgent safety restrictions, and communication to patients and healthcare professionals;
k) Acting as a Pharmacovigilance contact point for the Authority and for Pharmacovigilance inspections.
l) Preparation of relevant documents for submission to the Authority

The QPPV shall delegate specific tasks, under supervision, to appropriately qualified and trained individuals. Such delegation shall be documented.

3. Responsibilities of health facilities and pharmaceutical outlets

The healthcare facilities and pharmaceutical outlets shall in collaboration with the Authority, carry out the following responsibilities.

a. The healthcare facilities and pharmaceutical outlets shall establish a system for collecting, managing and reporting adverse reactions to the Authority.
b. The Healthcare facilities and pharmaceutical outlets shall appoint a focal person for coordination of Pharmacovigilance activities within their facilities.
c. The facilities shall perform the following functions-
    i. Receive and distribute adverse events reporting forms to healthcare providers;
    ii. detect, investigate, manage, and report adverse events and take appropriate action to prevent their occurrence;
    iii. Maintain a register of suspected adverse reactions, therapeutic failures, overdose, quality defective products, medication errors and drug interactions.

iv. Communicate appropriate safety information to health management teams and the community including patients.
v. conduct preliminary identification of signals and other risk factors;
vi. Organize and conduct staff training and sensitization on Pharmacovigilance
vii. Integrate the Pharmacovigilance concept into relevant committees, including hospital therapeutic committees and other health committees.

4. Responsibilities for County and Regional health management teams

Regional and County Health Management Teams shall plan, budget, and supervise the implementation of Pharmacovigilance activities within their regions and counties and ensure reports are submitted to the Authority on a quarterly basis.

5. Responsibilities of the public health programs

a. The public health programs shall have the following responsibilities regarding the safety of the products distributed within their programs-
   i. Identify focal persons to coordinate Pharmacovigilance activities;
   ii. Plan and budget for Pharmacovigilance activities;
   iii. distribute reporting forms, collect and analyse safety data for products used in their programs;
   iv. Risk management and follow-up of patients;
   v. reporting of adverse events to the Authority for the products used within their programs;
   vi. Collaborate with the Authority in implementing Pharmacovigilance activities, including training of health care providers on Pharmacovigilance ;
   vii. promote rational and safe use of products by health care providers;
   viii. educate and inform patients about their programs on the importance of reporting adverse reactions; and
   ix. Assess and communicate risks and effectiveness of the products.

6. Requirements for regional and county Pharmacovigilance Centers

a. The Pharmacovigilance Regional Centers shall work in collaboration with the Authority in coordinating the following Pharmacovigilance activities in the respective zones or regions
   i. receiving safety information, responding to queries and provide information related to Pharmacovigilance within the respective zones or regions;
   ii. receive and distribute reporting forms and collect data from health facilities
   iii. analyze adverse reaction reports and feed information into the data management tool where accessible and send them to Authority for further action;

iv. receive safety alerts from the Authority and share them with healthcare providers and patients in the respective zones;

7. **Requirements for Patients or Consumers for Reporting Adverse Drug Reactions and Events**

Patients or consumers play a crucial role in reporting Adverse Drug Reactions (ADRs) and Adverse Events (AEs) to improve medication safety. Below are the requirements and guidelines for reporting.

A. Who can report?

i. Any patient or consumer who experiences an ADR or AE.
ii. Caregiver or family members can report on behalf of a patient.

B. What information should be included in an ADR's report?

1. Patient Information
   I. Age, gender, and weight (if known)
   II. Underlying medical conditions
   III. Any known allergies
2. Description of the Adverse Reaction/ Event
   I. Symptom experienced (e.g., rash, nausea, dizziness, etc.)
   II. Severity (mild, moderate, severe, life-threatening)
   III. Time of onset (when the reaction started after taking the drug)
   IV. Drug of the reaction
3. Drug Information
   I. Name of the drug (brand or generic)
   II. Dosage and frequency taken
   III. Route of administration
   IV. Duration of drug use before the reaction occurred
4. Other Medication on Supplements Taken during the Period
   I. Any additional medicines, vitamins, or herbal supplements taken
   II. Possible drug interactions

5. **Action Taken**

I. Did the patient stop taking the drug?

II. Any medical treatment received (hospitalization, antidote, etc.)?

III. Outcome (Did the symptoms improve, worsen, or persist?)

C. Where to Report ADRs?

I. National Pharmacovigilance Center (Liberia Medicines & Health Products Regulatory Authority, LMHRA)

II. Online reporting portals of the Liberia Medicines & Health Products Regulatory Authority

III. Hotline numbers of the LMHRA

IV. Healthcare Providers (Doctors, Pharmacists, Nurses, etc.) at Facilities.

D. Importance of ADRs Reporting

I. Helps the Authority to monitor the safety of medicines

II. Assist in updating drug safety information to the VigiBase

III. Prevents harm to other patients by identifying dangerous ADRs.

Section 3: Pharmacovigilance inspections and auditing

1. Pharmacovigilance Inspections

a. The Authority shall conduct announced and unannounced inspections at any manufacturer, marketing authorization holders, and pharmaceutical facilities at all reasonable times for the purposes of ensuring compliance with good pharmacovigilance practice.

b. The inspection shall include the premises, records, documents, and PSMF of the Marketing Authorization Holder or any firms employed by the marketing authorisation holder to perform the activities.

c. Without prejudice, the inspection shall also involve review of procedures, systems, personnel, product-related Pharmacovigilance issues, and facilities to determine their compliance with regulatory Pharmacovigilance obligations.

d. The manufacturers and marketing authorisation holders shall be required to provide, on request, the PSMF, which will be used to inform inspection conduct.

e. The Pharmacovigilance system master file shall be permanently and immediately available for inspection at the site where it is kept.

f. If the PSMF is kept in electronic form, the data stored in electronic form shall be directly available at the site where the Pharmacovigilance system master file is kept.
g. The inspections shall include system and product-related inspections, routine inspections, "for cause" inspections, pre- and Post-authorisation inspections, announced and unannounced inspections, re-inspections, and remote inspections.
h. The scope of inspections shall include, but is not limited to, the following elements, as appropriate-
    i. collection, assessment, follow-up, documentation, record keeping, and archiving of Individual case safety reports (ICSRs);
    ii. completeness, accuracy, analyses, submission timelines
    iii. Safety evaluation of the Periodic Safety Update Reports (PSURs); and
    iv. Performance of the Pharmacovigilance system.
    v. ongoing safety evaluation
    vi. Interventional (when appropriate) and non-interventional CTs
    vii. QPPV involvement and awareness of product-specific issues
    viii. In-depth examination of processes, decision-making, communications, and actions relating to a specific trigger and/or product

i. The results of an inspection shall be provided to the inspected entity, who will be allowed to comment on any non-compliance identified within timelines prescribed by the Authority. Any non-compliance shall be rectified promptly through the implementation of a corrective and preventive action plan.
j. Inspection findings shall be graded as critical, major, and minor to indicate their relative criticality to risks impacting the Pharmacovigilance system, processes, and parts of processes.

2. Pharmacovigilance Self-audits

a. The manufacturers and marketing authorization holders shall establish processes to monitor the performance and effectiveness of a Pharmacovigilance system and including risk-based audits of their quality systems.
b. The risk-based audits of the Pharmacovigilance system shall cover all areas stipulated under these Regulations.
c. The risk-based audits of the quality system shall be performed at regular intervals to ensure that the quality system complies with the quality system requirements set out in these regulations to determine its effectiveness.
d. Risk assessment shall be documented appropriately for the strategic, tactical and operational planning of Pharmacovigilance audit activity in the organization.
e. Individuals who have no direct involvement in or responsibility for the matters or processes being audited shall conduct audits.

f. The corrective actions, including a follow-up audit of deficiencies, shall be taken where necessary.
g. A report on the results of the audit shall be drawn up for each audit and follow-up audit. The results of the audits and follow-up audits important findings shall be noted in the PSMF.
h. The issues that need to be urgently addressed shall be communicated in an expedited manner to the auditee's management and the upper management.
i. The management of the organization shall be responsible for ensuring there is a mechanism in place to adequately address the issues arising from Pharmacovigilance audits. Actions shall include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.
j. The audit shall involve evaluating the effectiveness of actions taken with the products for the purpose of minimizing risks and supporting their safe and effective use in patients;
k. The organization shall use performance indicators to monitor the good performance of Pharmacovigilance activities.

Section 4: Risk Management Systems

1. Establishment of the risk management system

a. The manufacturers and marketing authorization holders shall be required to establish a risk management system as a condition to the marketing authorization.
b. The manufacturers and marketing authorization holders shall be responsible for having an appropriate risk management system in place.
c. The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.
d. The system shall include risk minimization activities
e. The marketing authorization holders shall plan a risk management system very early on in a product's life cycle, including characterization and minimization of the risks associated with the product in the post-authorization phase.
f. The marketing authorization holders may be requested by the Authority to submit a RMP focused on the safety concern(s).
g. The risk management plans shall contain the following information-
    i. Products overview
    ii. Safety specification
    iii. epidemiology of the indication(s) and target population;
    iv. non-clinical part of the safety specification;
    v. clinical trial exposure;
    vi. populations not studied in CTs;

vii. post-authorization experience
viii. additional requirements for the safety specification;
ix. identified and potential risks;
x. summary of the safety concerns;
xi. Pharmacovigilance plan (including post-authorisation safety studies);
xii. plans for post-authorisation efficacy studies;
xiii. risk minimization measures (including evaluation of the effectiveness of risk minimization activities); and
xiv. summary of the risk management plan
xv. annexes

h. Ensuring that the knowledge and understanding on the product's safety profile, following its use in clinical practice, are critically reviewed.
i. The marketing authorization holder shall monitor Pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of the products.
j. The marketing authorization holder shall update the risk management system and the RMP accordingly
k. Provide a critical review of the safety profile of the product continuously, and this shall be reflected in data submitted with periodic safety update reports.
l. The guidance on templates and submission of RMPs shall be kept up-to-date on the Authority website.

Section 5: Collection, management, and reporting requirements for adverse events

1. Duty to Report Adverse Events, Adverse Drug Reactions, AEFIs, AESIs

Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days.

The healthcare facilities, public health programs, manufacturers, Marketing Authorization Holders, or any other designated person shall have a duty to report any of the following to the Authority-

a) all suspected Adverse Drug Reactions as a result of prescription and non-prescription;
b) unexpected reactions, regardless of their nature or severity, whether or not consistent with product information or labelling;

c) all adverse drug reactions regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product;
d) all adverse events following immunization or use of biological;
e) all adverse events, incidences, malfunctions associated use of medical devices or vitro diagnostic medical devices;
f) an observed increase in frequency of a given reaction;
g) a serious reaction, whether expected or not;
h) all suspected Adverse Drug Reactions associated with drug-drug, drug-food or drug-food supplement interactions;
i) adverse Drug Reactions in special field of interest including drug abuse and drug use in pregnancy and during lactation;
j) adverse Drug Reactions occurring from overdose or medication errors;
k) unusual lack of efficacy or when suspected quality defects are observed; and
l) Product quality problems.
m) All reports of unusual failure in efficacy shall be reported to the Authority by Marketing Authorization Holder, healthcare providers, public health programs using the ADR reporting form prescribed in the First Schedule to these Regulations.
n) Medication errors that arise during routine clinical practice shall be reported to the Authority using the Adverse Drug Reaction reporting form.

2. Requirements for Patients or consumers for reporting adverse drug reactions and events

Patients or consumers may report any suspected adverse reaction or event associated with the use of a product immediately to the nearest health facility, healthcare provider or directly to the Authority by using the Adverse Drug Reaction reporting form.

3. Reporting requirements for healthcare providers

a. Health care providers shall be obliged to report to the Authority all suspected adverse reactions, events or incidences reported by patients and any quality defect issues that may arise as follows-
    i. in case of suspected adverse reactions, events or incidences shall be as provided in the First Schedule;
    ii. in case of filled in suspected adverse reactions, events or incidences from patients in shall be as provided in the Second Schedule.
    iii. in case of any quality defect issues that may arise shall be as provided in the Quality Defect Form (QDF) of the Third Schedule to these Regulations; and
b. All healthcare providers shall be required to record Patients' Serious Adverse Reaction that are caused by allergic reactions to a product in the Poor Quality Medicinal Products Reporting Form (PQMPRF).

4. Requirements for adverse events reporting by manufacturers and marketing authorization holders

a. Without prejudice to the establishment of the Pharmacovigilance system and quality system provided under these Regulations, all manufacturers and marketing Authorization holders shall be required to report to the Authority any adverse reactions or events suspected to be associated with the use of their products notified to them by healthcare professionals, patients or consumers.
b. The adverse events reports shall include reports that arise from post-marketing experience, unsolicited and solicited sources, CTs, non-interventional post-registration studies, and other post-marketing studies and programs.
c. The reports shall meet requirements for reporting and recordkeeping stipulated in these Regulations.
d. Every manufacturer and marketing Authorization holder shall regularly screen the internet, including websites, webpages, blogs, vlogs, social networks, internet forums, chat rooms, and health portals or digital media for potential reports of suspected adverse reactions.
e. Every manufacturer and Marketing Authorization Holder shall report all suspected adverse reactions from medical and non-medical sources within the time specified in these Regulations.
f. All manufacturers and marketing authorization holders shall systematically assess the reports to establish a relationship to the product.
g. All manufacturers and marketing authorization holders shall regularly monitor international and domestic literature, ongoing safety and efficacy studies for any identification of adverse reaction reports or relevant safety findings regarding their products.

5. Reporting and field investigation of Adverse Events Following Immunization

a. Every healthcare worker or any person responsible for immunization or vaccination at the district or regional level shall be required to report to the Authority all Adverse Events Following Immunization (AEFI) of a vaccine or biological product using the prescribed AEFI reporting form.
b. AEFI shall include vaccine reactions, immunization error-related reactions, anxiety related immunization reactions and incidental events.
c. The Authority in collaboration with Program responsible for Immunization and Vaccine Development or as the case may be, shall conduct field investigation of the AEFIs for the following purposes:
    i. to confirm the reported diagnosis or propose other possible diagnoses as well as clarify the outcome of the medical incident comprising the AEFI;

ii. to ascertain the particulars, circumstances and procedures around the vaccine used to immunize the affected recipient, identify any potential vaccine related link to the given AEFI;
iii. to examine the operational aspects of the program, even if an event seems to be vaccine product induced or coincidental;
iv. to determine whether a reported event was a single incident or one of a cluster and if it is a cluster, confirm that the suspected immunizations were indeed given and the individual vaccines that were used; or
v. to determine whether unimmunized people are experiencing the same medical incidents.

d. Field investigation for different stakeholders and causality assessment of the events shall be conducted as described in the guidelines for surveillance of adverse events following immunization.
e. In case of vaccine-related reactions, the following actions shall be taken by the Authority-
i. Withdrawal of the lot with a higher reaction rate than expected;
ii. Investigate in collaboration with the manufacturer to identify the root cause;
iii. Suspension, de-registration, or cancellation of registration if the benefit-risk balance is not favourable.
f. In case of Immunization error-related events, the following error correction measures shall be taken by the Immunization program:
i. changing logistics for supplying the vaccine;
ii. Changing procedures at the healthcare facility;
iii. training of healthcare workers; and
iv. Intensifying supervision.
g. Notwithstanding, also in adherence with the above-mentioned in Regulation 7, the Authority may designate or authorize officers responsible for immunization and vaccine development assigned by the Ministry for the time being responsible for health to report all AEFIs to the Authority.
h. The Authority shall be required to communicate with parents, other members of the community, healthcare staff, and media regarding AEFI to keep them informed about the investigation, results, and action taken already or going to be taken regarding the AEFI.

6. Requirements for Expedited Reporting and reporting timelines

a. All serious adverse reactions associated with the use of a product shall be reported on an expedited basis.
b. The expedited reporting of serious reactions shall be as soon as possible, but in no case later than 15 calendar days of initial receipt of the minimum information. In case all the information needed is not available within 15 days, the Applicant should submit an initial report containing at least the minimum data elements required (i.e., patient details, suspected product details, reaction details and the reporter details) in order to meet the expedited reporting time

frames. A follow-up report containing more detailed information should be submitted later as soon as this becomes available.

c. For fatal or life-threatening, unexpected events during clinical development, the principal investigator (PI) is required to alert to the Authority as soon as possible but no later than 7 calendar days after first knowledge by the investigator that a case qualifies, followed by a complete report as soon as possible within 8 additional calendar days.
d. Every serious suspected adverse reaction occurring in all post- marketing studies of which the manufacturer is aware shall be reported to the Authority on an expedited basis.
e. A case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified
f. The reporting time shall be considered to begin again for submission of the follow-up report if any medically relevant information is received for a previously reported case.
g. The management of the adverse reactions shall follow good case management practice to ensure are authentic, accurate, as complete as possible, and non-duplicative.

Section 6: Periodic Safety Update Reports/Periodic Benefit-Risk Evaluation Reports and Development Safety Update Reports

1. Requirements for Periodic Benefit Risk Evaluation Reports/periodic safety update reports

a. Every marketing authorization holder shall submit to the Authority periodic safety update and Benefit-Risk Evaluation Reports for their products in the following cases-
b. where such obligation has been prescribed by the Authority as a condition during marketing authorization of a product;
c. when requested by the Authority based on concerns relating to Pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorization has been granted;
d. The reports shall be submitted to the Authority immediately upon request or in accordance with the following-
    i. where a product has not yet been placed on the market, at least every 6 months following authorization and until the placing on the market;
    ii. where a product has been placed on the market, at least every six months during the first two years following the initial placing on the market, once a year for the following two years and at three yearly intervals thereafter;
    iii. The dates of submission according to the specified frequency shall be calculated from the date of the authorization of the product.
e. The periodic benefit risk evaluation reports/ periodic safety update reports shall contain at a minimum the following-

i. summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization;
ii. a scientific evaluation of the risk-benefit balance of the medicinal product
iii. all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorization holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.
iv. collection of adverse drug reaction (ADR) information (i.e. local serious ADRs, local non-serious ADRs, foreign serious ADRs, foreign non-serious ADRs, case reports published on international or local literatures including academic conferences);
v. The Periodic Benefit Risk Evaluation Report shall contain a comprehensive, concise, and critical analysis of product's known or emerging important risks and to evidence of emerging important benefits including the following-
vi. summary of relevant new safety information that could have an impact on the benefit-risk profile of the product;
vii. summary of any important new efficacy or effectiveness information that has become available during reporting interval;
viii. assessment of whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the product's benefit and risk profile;
ix. conducting an integrated benefit-risk evaluation for approved; indications in case a new safety information that has emerged;
x. Recommend action to optimize the benefit-risk profile.

f. The PSUR/PBER reports shall be submitted both in hard copy and soft copy in electronically.

2. Development Safety Update Reports (DSURs)

Every Sponsor and Marketing Authorization Holder shall be required to submit to the Authority the periodic Development Safety Update Report (DSUR) on drugs under development including marketed drugs that are under further study. These report should be summited on an annually basic.

a) Per investigational drug, a single DSUR shall be prepared with date pertinent to all dosage forms and strengths, all indications, and all patient populations under study with the investigational drug, wherever feasible. If this is not possible an explanation should be provided in the introduction section of the DSUR
b) If more than one sponsor is involved in drug development, a single DSUR can be submitted.
c) The DSUR shall provide safety information from all ongoing CTs and other studies that the sponsor is conducting or has completed during the review period including-
    i. CTs using an investigational drug such as human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I to III);

ii. clinical trials conducted using marketed drugs in approved indications such as therapeutic use trials (Phase IV);
iii. therapeutic use of an investigational drug;
iv. clinical trials conducted to support changes in the manufacturing process of medicinal products;
v. any significant other findings pertinent to the safety of the investigational drug.

Section 7: Signal Management

1. Signal Detection, Identification, and Management

a. The Authority shall perform the initial analysis and prioritization of signals of new risks that have changed or changes to the risk-benefit balance.
b. Subject to subsection (1), where the Authority considers that follow-up action may be necessary, the assessment of the signals and agreement on any subsequent action concerning the marketing authorization shall be conducted in a timescale commensurate with the extent and seriousness of the issue.
c. Every manufacturer and marketing authorization holder shall be required to have in place mechanisms for signal detection and investigation, including the following –
    i. have a system in place for detecting and investigating safety issues (or signals) that may arise at any stage in the life cycle of a product, including the clinical development, manufacturing or in the post-market setting, promptly;
    ii. have written procedures in place that adequately describe the way in which the MAH shall perform signal detection;
    iii. The roles and responsibilities of each person involved in the signal detection process shall be identified and documented.
    iv. The source of the information to include in the analysis and the method used for signal detection shall be documented;
    v. Actions taken based on the outcome generated from the signal detection activities shall be documented adequately;
    vi. Data regarding changes of what is known about the risks and benefits of the drug shall be sent to the Authority and shall be documented; and
    vii. Safety monitoring activities shall include a review of cumulative cases, in order to allow for a comprehensive review of potential safety issues.
    viii. Continuously monitor the data to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the risk-benefit balance of the medicinal product.
    ix. They should validate and confirm signals, as appropriate, based on an examination of individual case safety reports, aggregated data from active surveillance systems or studies, literature information or other data sources.

Section 8: Post-Authorization Studies

1. **Requirements for Post-authorization safety studies**
   a. The Authority may act on recommendations from results derived from post-authorization studies conducted on safety and efficacy as a condition at the time of the granting of the marketing authorization.
   b. The post-authorization study shall be registered in accordance with the regulations for Control of CTs in force.
   c. The marketing authorization holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the product concerned.
   d. Every new information that may affect the risk-benefit balance of the product shall be communicated immediately within 14 days in writing as an emerging safety issue to the Authority.
   e. The communication under this section shall, without prejudice to the information on the findings of studies, be provided by means of Periodic Safety Update Reports (PSURs).
   f. Individual cases of suspected adverse reactions and Serious Adverse Events that arise from the studies shall be reported to the Authority according to the requirements set out in the regulations for conduct of Clinical Trials in force.
   g. A quarterly progress report on the studies shall be submitted to the Authority;
   h. Final study report shall be submitted to the Authority within twelve (12) months of the end of data collection.
   i. The marketing authorization holder shall ensure the fulfilment of its Pharmacovigilance obligations in relation to the study may be audited, inspected and verified.
   j. Information on studies conducted pursuant to an obligation imposed by the Authority shall be included in the risk management plan.
   k. The Authority shall from time to time conduct its own post marketing surveillance studies if deemed relevant to determine safety, quality and effectiveness of the products placed on the market.

Section 9: Pharmacovigilance of Other Products

1. **Reporting of medical devices adverse events, incidences and malfunctions**
   a. All operators, users, distributors, healthcare workers, manufacturers and marketing authorization holders shall be required to report to the Authority all adverse events or incidences associated with use of the medical devices
   b. All Marketing Authorization Holders shall be required to ensure that there is collection, analysis and evaluation of risks arising from the use of their medical devices, in particular, adverse effects, interactions with other substances or products, contra-indications,

falsifications, operational defects, malfunctions and technical defects and the necessary measures to be taken.

c. The collection, analysis, report management, timelines, and reporting requirements shall be as provided in the medical devices control regulation in force and the guidelines for medical devices vigilance applicable.

2. Reporting of Adverse Events following Cosmetic Use

a. A cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use.

b. All manufacturers, Marketing Authorization Holders, and distributors of cosmetics shall be required to report to the Authority the following-

   i. all serious undesirable effects which are known to him or which may reasonably be expected to be known to him;
   ii. the name of the cosmetic product concerned, enabling its specific identification;
   iii. The corrective measures taken by him, if any.
   iv. The nature of the alleged SUE and the date of its onset;
   v. If the minimum information cannot be obtained, the notifier should continue to undertake all reasonable efforts to obtain the information and notify without delay as it becomes available. The existence of SUE cannot be confirmed unless a minimum amount of information can be obtained.

c. The reports shall be submitted to the Authority within fourteen (14) days from the date they become aware of the serious undesirable effects or AE

d. Where end users report serious undesirable effects to health professionals, they shall immediately transmit the information to the Authority.

e. In the event of serious doubt regarding the safety of any substance contained in cosmetic products, in which a product containing such a substance is made available on the market, the Marketing Authorization Holder and manufacturers shall submit a list of all cosmetic products for which he is responsible and which contain such substance.

f. The list referred to under sub-regulation (4) shall indicate the concentration of the substance in the cosmetic products.

g. The responsible persons (including the manufacturers) shall be required to take all appropriate measures, including corrective actions bringing the cosmetic product into conformity, the withdrawal of the product from the market or its recall, within an expressly mentioned time limit, commensurate with the nature of the risk.

h. The manufacturers and marketing Authorization Holders shall be required to conduct investigations as requested by the Authority.

i. The manufacturers and marketing Authorization Holders shall be required to establish a Cosmetovigilance system and to a management and communication system on serious undesirable effects to monitor the safety of their products in the market.
j. The manufacturers and marketing Authorization Holders shall submit to the Authority annual Cosmetics Product Safety Report (CPSR) as required.
k. The report shall be accompanied with a causality assessment report to determine whether a notified serious undesirable event is considered to be attributable to the use of a cosmetic product.
l. The manufacturers and marketing Authorization Holders shall undertake corrective actions following assessment of the post marketing surveillance data, together with other sources of safety data.
m. The Authority shall conduct market surveillance, market analysis, evaluation, and end user information and evaluation of trend and signal analysis.
n. The Authority shall ensure that responsible persons who consider or have reason to believe that a cosmetic product which they have placed on the market is not in conformity with this Regulation shall immediately take the corrective measures necessary to bring that product into conformity, withdraw it or recall it, as appropriate.
o. Furthermore, where the cosmetic product presents a risk to human health, responsible persons shall immediately inform all stakeholders in the pharmaceutical sectors where the products are made available, giving details, in particular, of the non-compliance and of the corrective measures taken.

3. Reporting of adverse events on the use of antiseptics and disinfectants

a. Every manufacturer and Marketing Authorization Holder shall be required to report adverse reactions associated with the use of antiseptics and disinfectants using the First Schedule prescribed in these regulations in their conventional paper forms or electronically.
b. The reporting requirements and timelines shall be as stipulated in these Regulations.

4. Reporting of adverse events in clinical trials

Reporting of serious adverse events and Serious Unexpected Adverse Drug Reactions occurring in CTs shall comply with the requirements stipulated under the Clinical Trials Control Regulations in force.

5. Reporting of falsified and or substandard products

a. Where medicines, biologicals, medical devices, herbal medicines, antiseptics and disinfectants are suspected to be falsified or substandard, the marketing authorization holder, distributor, healthcare professional or any other person shall be required to report to the Authority using a form specified in the Third Schedule of these Regulations

b. A person shall not deal in any medicine or vaccine that is confirmed to be a substandard or falsified.
c. The Authority shall investigate and confiscate if a product is suspected to be a substandard or falsified.
d. The Authority shall require the manufacturer and marketing authorization holder to conduct extra monitoring of their products and submit reports if it determines that a medicine or vaccine is suspected to be substandard or falsified.

Section 10: Regulatory Actions

1. Suspension of Registration

a. The Authority shall ensure that healthcare professionals are rapidly informed of its action and the reasons for the action. Networks set up by professional associations may be used to this effect for the timely dissemination of medical information.
b. The Authority shall cancel or suspend registration of the product that fails to comply with the conditions of these Regulations.

2. Notice of suspension

a. Any suspension shall be effected upon a written notice thereof.
b. The notice for suspension of registration of a medicinal product as set out in the Regulations for Registrations of Medicinal Products in force.
c. In additional to the reasons for suspension, the notice shall state any corrective action required to be taken and the time within which it must be taken.
d. Before suspension, the Authority shall require the marketing authorization holder to show cause as to why the suspension should not be effected.

3. Suspension or cancelation of registration without Notice

a. The Authority may cancel or suspend the registration of a medicinal product without prior notice if it is necessary to do so in order to prevent injury to the health or safety of patients, users or other persons.
b. The marketing authorization holder may apply to the Authority, in writing, that the cancelation or suspension be uplifted.
c. The Authority shall, within forty-five (45) days after the date of receiving the application, review its decision.

4. Restoration of Registration

Pursuant to the provision of these regulations, the Authority may, upon satisfaction that the reason giving rise to the suspension or cancellation of registration has been corrected or if

such reason for suspension or cancelation was unfounded, reinstate the registration of a medicinal product.

5. Cancellation or revocation of marketing Authorization

a. The Authority may cancel or revoke the marketing authorization of a registered medicinal product if-
   i. the medicinal product no longer meets the quality, safety and effectiveness requirements; and
   ii. The marketing authorization has been suspended for a period of more than twelve (12) months.

b. Under the provision of sub-regulation (1), a written notice of cancellation shall be issued to the marketing authorization holder stating the reasons for cancellation.

6. Offence

a. Any person who contravenes any provision of these Regulations or directly or indirectly aids any other person to do what is prohibited under these Regulations commits an offence and shall be punished by the provisions under the Act.

b. Any MAH/ institution/ healthcare provider who fails to notify the Authority of adverse reactions and adverse events commits an offence under the Act and upon conviction shall be liable to a fine or imprisonment, or any legal action under the Act.

7. Penalty

Any person found in violation of these Regulations shall be liable to the sanctions as prescribed in the LMHRA Act.

8. Review and Appeals

a. Any person aggrieved by a decision of the Authority may, within sixty (60) days from the date of notice, apply for review or reconsideration of the decision to the Authority showing grounds for dissatisfaction.

b. The Authority shall, within thirty (30) days from the date of receiving the application, review, reconsider, reject, or vary the decision.

c. Notwithstanding the provision of sub-regulation, the applicant shall not be barred from appealing to the Director of Pharmacovigilance & CTs without applying for review or reconsideration to the Authority.

9. Procedure of appeal

a. Notwithstanding the provisions of the regulation above, any person aggrieved by a decision of the Authority may, within sixty working days, appeal in writing to the Director of Pharmacovigilance & Clinical Trials.
b. The appellant shall send a notice of the appeal to the Authority, which shall, within fourteen (14) working days, submit a written response to the Managing Director for perusal.
c. Where the **Managing Director** thinks that a case has been made, he/she may summon the parties for additional information or make a decision to allow or dismiss the appeal.
d. The decision of the Managing Director made under sub-regulation (bullet 3) shall be final.

10. Recognition

The Authority may, upon proof of scientific information received relating to the safety of medicines and health products from other regulatory authorities or relevant international bodies, make a regulatory decision or a regulatory action to protect the public of Liberia from any imminent safety concerns that may likely arise.

Part III

Section 1: Annex I

LMHRA may use international guidelines and other applicable legislations in line with the country legislation for pharmacovigilance of medicinal products, including vaccines, herbal medicines, gene therapy products, ATMPs, and medical devices. Legislation and guidelines relied upon include, but are not limited to:

EU Legislative documents

- Directive 2010/84/EU
- Regulation (EU) No 1235/2010
- Commission Implementing Regulation (EU) No 520/2012
- Regulation (EU) No 1027/2012
- Directive 2012/26/EU
- Consolidated version of Directive 2001/83/EU
- Consolidated version of Regulation (EC) No 726/2004
- Commission Delegated Regulation (EU) No 357/2014 on post-authorisation efficacy studies
- Volume 9A of the Rules Governing Medicinal Products in the EU

EU guiding documents

- Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems
- Guideline on good pharmacovigilance practices (GVP) - Module II – Pharmacovigilance system master file (Rev 2)
- Guideline on good pharmacovigilance practices (GVP) Module III – Pharmacovigilance inspections (Rev 1)
- Guideline on good pharmacovigilance practices (GVP) Module IV – Pharmacovigilance audits (Rev 1)
- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)
- Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
- Guideline on good pharmacovigilance practices (GVP) - Module VI Addendum I – Duplicate management of suspected adverse reaction reports
- Guideline on good pharmacovigilance practices (GVP) - Module VII- Periodic Safety update Reports

- Explanatory Note to GVP Module VII Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1)
- Module VIII – Post-authorisation safety studies (Rev 3) Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 3) (europa.eu)
- Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3) 58 GVP Module VIII Addendum I Rev 3 - Final published (europa.eu)
- Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions Guideline on good pharmacovigilance practices (GVP) - Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions
- Module IX – Signal management (Rev 1) Guideline on good pharmacovigilance practices (GVP) - Module IX – Signal management (Rev 1)
- Module X – Additional monitoring GVP Module Additional Monitoring (europa.eu)
- GVP Product-or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations I Vaccines for prophylaxis against infectious diseases (europa.eu),
- GVP Product- or Population-Specific Considerations III: Pregnant and breastfeeding women Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (europa.eu),
- Guideline on clinical evaluation of vaccines Guideline on clinical evaluation of vaccines (europa.eu)
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. Guideline on the exposure to Medicinal Products during pregnancy
- Good practice guide on recording, coding, reporting and assessment of medication errors Good practice guide medication error recording coding reporting assessment (europa.eu)
- Detailed guidance on ICSRs in the context of COVID-19 Detailed guidance on ICSRs in the context of COVID-19 - Revision 3 (europa.eu)
- Consideration on core requirements for RMPs of COVID19 vaccines CoreRMP19 Requirements for Covid-19 vaccines (europa.eu)
- Consideration on core requirements for PSURs of COVID-19 vaccines corePSUR19 requirements for COVID-19 vaccines (europa.eu)

ICH Guidelines

- E1: _Guideline for the extent of population exposure to assess clinical safety
- E2A: _ Guideline Clinical Safety Data Management Definitions and standards for expedited reporting.
- E2B:_R3__IWG_Concept_Paper_10_July_2013 Electronic submission of ICSRs
- E2C: _ R2_Step4 Periodic Benefit -Risk Evaluation Report (PBRER)
- E2D: _ Guideline Post approval safety data management- Definitions and standards for expedited

- reporting
- E2E:_Guideline Pharmacovigilance Planning
- E2: Clinical Safety Data Management
- E6: Good Clinical Practice: Consolidated Guideline
- E11: Clinical Investigation of Medicinal Products in the Pediatric Populations
- E11 (R1) Addendum to ICH E11: Clinical Investigation of Medicinal Products in the
- Pediatric Population E11(R1)
- M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Q1: Stability Testing
- Q2: Validation of Analytical Procedures
- Q3: Impurity Testing

Section 2: References

1. The LMHRA Act 2010 establishing the Liberia Medicines and Health Products Regulatory Authority
2. Guideline for the National Pharmacovigilance System (February, 2009) The Pharmacy and Poisons Board: Ministry of Health, Republic of Kenya
3. Roger Walker and Clive Edwards. Clinical Pharmacy and Therapeutics. (1999); 2: 33-45
4. Safety of Medicines in Nigeria- a guide for detecting and reporting ADRs, NAFDAC- NPC-NIG-2004.1
5. WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre. Safety Monitoring of Medicinal Products- Guidelines for setting up and running a Pharmacovigilance Center (2012)
6. WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre. The Importance of Pharmacovigilance - Safety monitoring of medicinal products (2002)
7. WHO Quality Assurance and Safety. Aide Memoire- for a national strategy for safe drugs and their appropriate use.
8. WHO Policy Perspectives on Medicines. Pharmacovigilance: ensuring the safe use of medicines. October 2004.
9. WHO Safety of Medicines - a guide to detecting and reporting adverse drug Reactions: WHO/EDM/QSM/2002.2
10. ICH (2004). *Pharmacovigilance planning*. [online] Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf [Accessed 10 Mar. 2017].
11. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf)

These Regulations shall become effective immediately upon approval by the Chairman of the Board of Directors.

The Regulations for Pharmacovigilance in Liberia are hereby promulgated and submitted by the Managing Director of the Authority on this 26th day of September A.D. 2024 to the Board of Directors for approval.

Hon. Luke L. Bawo, Jr.
Managing Director / LMHRA

The Regulations for Pharmacovigilance in Liberia are hereby approved by the Chairman of the Board of Directors for Approval.

Approved This 3rd Day of October A. D. 2024

Dr. David Sumo
Chairman / Board of Directors